UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,521	02/18/2005	Gideon Schreiber	05558.0018.PCUS00	7709

22930 7590 11/21/2005

HOWREY LLP
C/O IP DOCKETING DEPARTMENT
2941 FAIRVIEW PARK DR, SUITE 200
FALLS CHURCH, VA 22042-2924

EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/500,521	SCHREIBER, GIDEON	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62-86* is/are pending in the application.

4a) Of the above claim(s) *84 and 86* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62-83 and 85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the preliminary amendment filed June 30, 2004, canceling claims 1-61 and adding new claims 62-86. The paper also amended the drawings and provided a substitute specification. Currently, claims 62-86 are pending.

Election/Restrictions

Pursuant to the interview of October 27, 2005with Applicant's representative (of record), the restriction requirement dated October 6, 2005 has been withdrawn. Applicant's election of species, with traverse, of alanine, SEQ ID NO: 2, autoimmune disease and multiple sclerosis is acknowledged.

Claims 84 and 86, directed to the non-elected species of viral disease and cancer, have been withdrawn by the examiner. The species restriction requirement is still deemed proper and is therefore made FINAL.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Israel on December 31, 2001. It is noted, however, that applicant has not filed a certified copy of the 147414 application as required by 35 U.S.C. 119(b).

Drawings

The drawings are acceptable.

Claim Rejections - 35 USC § 101-Non-Statutory Subject Matter

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 62-65, and 67-74 are rejected under 35 USC §101, as directed to non-statutory subject matter.

Claims 62, and 72-74 are directed to an IFNAR2 polypeptide mutated at positions His 78 and Asp 100. When the claims are given their broadest reasonable interpretation, the polypeptide receptor

is not isolated and purified and said mutations may have resulted spontaneously within the IFNAR2 gene, resulting in a mutated IFNAR 2 polypeptide that is a product of nature.

Claims 63-71 depend from claim 62.

Claim Rejections - 35 USC § 112, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 62-65, 67-83 and 85 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art (hereafter the Artisan), that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 62-65, 67-83 and 85 read on any alternative receptor form of IFNAR2 polypeptide from any species of animal that expresses an endogenous beta chain subunit of the type I IFN receptor. As such, the claims encompass any and all membrane bound or soluble forms of IFNAR2 polypeptides that may be isolated and mutated from any species of animal. The specification discloses the human form of IFNAR2 extracellular domain (identified in Figure 2 and SEQ ID NO: 2), that are mutated at positions His 78 and Asp 100, and designated IFNAR2-EC (Example 2). However, the specification provides no cross-species analysis to demonstrate that such receptors were included in the present invention. Moreover, Applicant's specification provides no examples of additional members of the variants of the IFNAR2 receptors. Claims 62-65 and 67-85 encompass a large number of receptor sub-type sequences that contain IFN-β binding activity and genes encoding IFNAR2 in different species of animals. Claims 62-65, 67-83 and 85 thus constitute a claimed genus that encompasses other polypeptide and genomic sequences that may encode an IFNAR2 receptor, yet to be discovered, and since the specification only discloses a single species (a **human** IFNAR2- **EC** polypeptide, as in SEQ ID NO:1 and Figure 2), the disclosed structural features of said receptor do not constitute a substantial portion of the claimed genus. As such, the Artisan of skill could not predict that Applicant possessed any additional species, except for the human IFNAR2-EC receptor. Hence, only the polypeptide sequence from the human IFNAR2 extracellular portion could be demonstrated as possessed.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

> [A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Applicant's attention is also directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan of skill could determine the desired effect. Hence, the analysis above demonstrates that Applicant has not determined the core structure for full scope of the claimed genus.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. Therefore, the breadth of the claims as reading on IFNAR2 receptor sequences yet to be discovered; in view of the level of knowledge or skill in the art at the time of the invention, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of the genus of IFNAR2 sequences containing all the variants of the receptor in all animal species (Claim 62). Thus it

is concluded that the written description requirement is not satisfied for the claimed genus. Claims 63-65, 67-80, 82-83 and 85 depend from claim 62.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of any and all membrane bound or soluble forms of IFNAR2 polypeptides that may be isolated and mutated from any species of animal; at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 112-Scope of Enablement

Claims 62-65, 67-83 and 85 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated **human** IFNAR2- **EC** polypeptide, comprising SEQ ID NO:1, wherein amino acid residues His 78 and Asp 100 of the extracellular domain are substituted with an amino acid residue, does not reasonably provide an enablement for the isolated and mutated polypeptide sequence of any and all receptor variants of the type I IFN receptors, that may be present in any species of animal (claim 62) as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

The Nature Of The Invention And Breadth Of Claims

Claim 62 is drawn to an IFNAR 2 polypeptide sequence, mutated at positions His 78 and Asp 100. Claim 63 further limits the His 78 mutation of claim 62 to alanine. Claim 64 further limits the Asp 100 mutation of claim 62 to alanine. Claim 65 further limits claim 62, to double substituted mutations at positions 78 and 100. Claim 62 encompasses any and all polypeptide sequences that comprise the IFNAR2 receptor variants isolated and mutated from any and all species of animals. The detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide knowledge, so that the Artisan of skill would be able to practice the invention as claimed by Applicant, without undue burden being imposed on such Artisan. This burden has not been met because it would require undue experimentation to isolate and mutate all polypeptide sequences that comprise the alternatively spliced receptor forms of IFNAR2 for all species of animals that may contain genes for IFNAR2 isoforms, as claimed in the instant application. Claims 63-65, 67-83 and 85 depend from claim 62.

The Unpredictability Of The Art And The State Of The Prior Art

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The state of the prior art is effectively summarized by the references of Pfeffer et al. (Interferon Therapy of Multiple Sclerosis pp. 1-39, 1997; Abstract); Piehler et al. (J. Mol. Biol. 294:223-237, 1999) and Hertzog et al. (PCT Publication No. WO 00/24417, 4 May, 2000).

The art teaches the isolation and sequence analysis of type I interferon receptor (Hertzog, p.2, second paragraph). The art also teaches that IFNAR polypeptides comprise a family of proteins produced by multiple mRNA transcripts that are translated into several isofroms (Hertzog, p.2, second paragraph). The art also teaches that mutations at positions His 78 or Asp 100 of the IFNAR2 extracellular domain affect the binding of the receptor to IFN-β (Piehler et al., p. 230, lines 8-15 and

Table 2, p. 229). However, the art does not teach the effect of a soluble IFNAR2 receptor for IFN-β when both His 78 and Asp 100 are mutated.

Claim 62 of the instant application is drawn to a broad IFNAR2 polypeptide sequence, mutated at positions His 78 and Asp 100, that is not apparent from the disclosure of the invention. The instant specification provides evidence that amino acid substitutions at just two sites (His 78 and Asp100) of the isolated human IFNAR2 EC domain can profoundly alter the affinity of the soluble receptor for IFN-β, thus affirming the criticality of the protein's sequence and primary structure in affecting secondary and tertiary folding and subsequent ligand binding activity. Because each alternatively spliced variant of IFNAR2 from all animal species (as claimed in claim 62), would comprise different polypeptide sequences, and hence different secondary and tertiary structures, it would require undue experimentation by the skilled Artisan to carry out multiple amino acid substitutions on all variants of said receptor from all animal species, and to further test the resultant mutated receptors for a synergistic increase in the affinity of said receptors for IFN-β, as claimed in claim 62. In view of the lack of teachings or guidance provided by the specification with regard to enabled, mutated IFNAR2-EC sequences from all species, encompassing all alternatively spliced variants, the lack of teachings or guidance provided by the specification to overcome the art-recognized unpredictability and difficulty inherent in isolation of said receptor variant sequences, and for the specific reasons cited above, it would have required undue experimentation for an Artisan of skill to make and use the claimed invention. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

The Amount Of Direction Or Guidance Presented And Working Examples

The specification fails to disclose adequate representations of isolated and mutated IFNAR 2 polypeptide sequences from all species of animals, encompassing all variants and isoforms of the receptor. The specification discloses a single species (a mutated, IFNAR2- **EC** polypeptide, as in SEQ ID NO:1 and Figure 2) and described in Example 2. However, the specification provides no cross-species analysis to demonstrate that such receptor polypeptide sequences were included in the present invention. Moreover, Applicant's specification provides no examples of additional members of the variant forms of the IFNAR2 receptor. The guidance provided by the specification amounts to an

invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses the mutated polypeptide sequence of one isoform of IFNAR2 from human.

Quantity Of Experimentation

The quantity of experimentation in this area is extremely large, as there are a significant number of parameters, which would have to be studied and tested to make and definitively show that one is in possession of all IFNAR2 receptor variants, that include alternatively spliced, membrane bound and soluble extracellular forms that may be obtained from all animal species that may harbor genes encoding IFNAR2 receptors. The task may require even further experimentation as polypeptide sequences may not share significant sequence homology across species to allow the same synergistic increase in affinity for IFN-β, as observed in the mutations of the instant invention. This would require a significant degree of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level Of Skill In The Art

The level of skill in the art at the time of invention is deemed to be high. However, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed without undue experimentation.

Analysis And Conclusion

Applicant is therefore enabled for an isolated **human** IFNAR2- **EC** polypeptide comprising SEQ ID NO:1, mutated at amino acid residues His 78 and Asp 100 of the extracellular domain, wherein said mutations synergistically increase the affinity for IFN-β relative to an isolated human non-mutated IFNAR2-EC polypeptide. In the instant case, as discussed above, in a highly unpredictable art where the isolation and analysis of all variants of IFNAR2 polypeptide sequences from all animal species, together with the large quantity of research required to define these unpredictable variables, and the lack of guidance provided in the specification, it is the position of the

examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112-Lack of Enablement

Claims 83 and 85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for a method of treating an autoimmune disease or multiple sclerosis, by administering to a patient in need of treatment for said diseases, a therapeutically effective amount of a composition comprising an IFNAR2 polypeptide mutated at residues His 78 and Asp 100.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, were recited *supra*.

The state of the prior art is effectively summarized by the references of Pfeffer et al. (Interferon Therapy of Multiple Sclerosis pp. 1-39, 1997; Abstract); and Hertzog et al. (PCT Publication No. WO 00/24417, 4 May, 2000). Pfeffer et al. teach that interferons are clinically useful in the treatment of various human diseases, including multiple sclerosis and that knowledge of the interactions between interferons and cells "[s]hould expedite the therapeutic use of interferon-beta and provide a basis for developing new strategies in the treatment of multiple sclerosis with interferon-beta alone or in combination with other agents" (Abstract). Hertzog et al. describe a method of regulating interferon type I functional activity by administering a soluble IFNAR2a soluble receptor (p.1, paragraph 1). Herzog also teaches that the role and contribution of IFNAR2, to ligand binding and signal transduction remains unknown (p. 2, paragraph 3) and that soluble IFNAR2a has been found to inhibit the functional activity of type I interferon (p.3, first paragraph).

The specification of the instant application discloses that results from one study have shown interferon beta administered intrathecally is effective in reducing the exacerbations of multiple sclerosis (p.4, paragraph 0010). The specification further describes that the advantages of using mutated IFNAR2EC are that it is possible to administer lower quantities of the receptor as a carrier and

because of the stabilizing activity of the mutant, it is possible to reduce the amount of IFNβ administerd. However, the specification also teaches that "in some inflammatory disorders, where it may be required to lower the IFN concentrations, it is possible under certain conditions to use this mutant as an effective antagonist specifically toward IFNβ" (p. 9, paragraph 0035). The specification fails to provide a description of what constitutes a therapeutically effective amount of a composition comprising the IFNAR2 mutated polypeptide and optionally an IFN antagonist, as recited in claims 83, and how an Artisan would differentiate between said therapeutic amount serving as a carrier for IFN versus an antagonist for IFN. The specification also fails to provide any examples wherein said composition has been administered to a patient having an autoimmune disorder or multiple sclerosis, either alone or in combination with IFN.

The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. The detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide knowledge, so that the Artisan of skill would be able to practice the invention as claimed by Applicant, without undue burden being imposed on such Artisan. The lack of teachings or guidance provided by the specification to overcome the art-recognized unpredictability and difficulty inherent in therapeutic treatment of autoimmune diseases, including multiple sclerosis, and for the specific reasons cited above, it would have required undue experimentation for an Artisan of skill to make and use the claimed invention. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 62-76 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Piehler et al. ((J. Mol. Biol. 294:223-237, 1999).

The claims embrace an IFNAR 2 polypeptide wherein amino acids at positions His 78 and Asp 100 are substituted by alanine, wherein said mutations synergistically increase the affinity for IFN-β. Piehler et al. describe an IFNAR 2 polypeptide wherein amino acids at positions His 78 or Asp 100 are substituted by alanine (Fig. 6A, p. 230, Table 2, p. 229). Piehler et al. further describe that "the mutant H78A stabilizes the complex with IFN-β nearly two fold, while destabilizing the complex with IFN-α2 more than twofold. The mutation N100A hardly affects the rates for binding IFNα2, whereas its decreasing dissociation rate constant for IFNβ by almost fourfold" (p. 230, lines 10-15). Therefore, the effects of mutations at positions His 78 and Asp 100 on the affinity of the receptor for IFN-β are described by Piehler et al.

Piehler et al. do not make an IFNAR2 receptor that has alanine substitutions at both positions His 78 and Asp 100, but directly provide the motivation to simultaneously introduce both mutations in the extracellular domain of IFNAR2. On page 234, second paragraph, column 1, Piehler et al. state: "It would be interesting to explore the phenotype of a H78, N100 double mutation in ifnar2, which should have about a 20-fold tighter binding for IFNβ compared to IFNα2. Therefore the express suggestion to substitute both mutations simultaneously at positions His 78 and Asp 100, provided the motivation to create mutations at positions that were already apparent in the prior art. Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to make the combination of mutations at positions 78 and 100 of IFNAR2, thus resulting in the practice of the instantly claimed invention. The state of the art at the time of the invention had demonstrated the effective use of mutant forms of IFNAR2 in altering IFNβ binding. The prior art had also shown the routine use of mutational and subsequent structural analysis of polypeptides. Therefore, an artisan of skill, having combined the elements of the mutations at positions His 78 and Asp 100 would have a reasonable expectation of success.

Claims 77-81 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Piehler et al. ((J. Mol. Biol. 294:223-237, 1999) as applied to claims 62-76 above, and further in view of Campbell et al. (U.S. Patent Publication No. US2001/001433, published Aug. 16, 2001).

The claims embrace a DNA encoding IFNAR 2 polypeptide wherein amino acids at positions His 78 and Asp 100 are substituted by alanine, wherein the encoded polypeptide comprising a signal

peptide sequence of human growth hormone that may be expressed in a vector in prokaryotic or eukaryotic host cells. The mutated forms of IFNAR2, their production in E. coli and isolation are described by Piehler (p. 235, under protein expression and purification). Piehler describes the lower yields of properly refolded infnar2-EC (approximately 20% compared to the wild-type; lines 10-12) for a number of the INFNAR2 mutants, thus providing the motivation to express IFNAR2 mutants in a paradigm that would enhance the production of INFNAR 2 mutant polypeptides. Piehler does not describe signal peptide sequences, including the hGH signal sequence or the use of eukaryotic cells for expression of INFNAR 2 mutants. Campbell describes fusion protein constructs containing the hGH signal peptide in place of the native signal sequence of proteins (p. 5, column 1, lines 2-5). Campbell further describes that the expression of the recombinant proteins mentioned can be effected in eukaryotic or prokaryotic cells (p. 3, paragraph[0038]). The prior art had also shown the routine use of expression vectors for production and purification of polypeptides in prokaryotic and eukaryotic cells. Therefore, an artisan of skill, having combined the elements of the mutated IFNAR2 DNA and the hGH signal peptide would have a reasonable expectation of success in expressing IFNAR2 polypeptide in a vector in prokaryotic or eukaryotic cells.

Conclusion

No claims allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Victor Barlow, whose telephone number is **(571) 272-0506**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00 am-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on **(571) 272-0731**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

For all other customer support, please call the USPTO Call Center (UCC) at **(800) 786-9199**.

Fereydoun G. Sajjadi, Ph.D.
Examiner, USPTO, AU 1633

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER